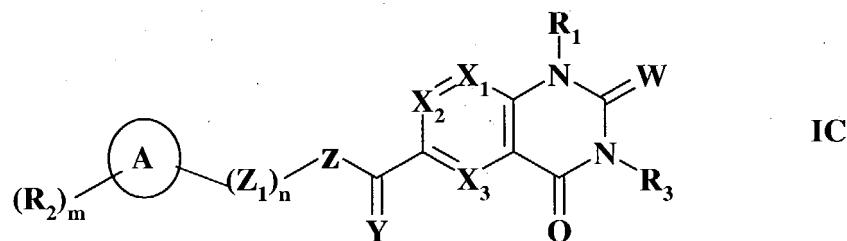


CLAIMS

What is claimed is:

1. A combination, comprising a selective inhibitor of COX-2 that is not celecoxib or valdecoxib, or a pharmaceutically acceptable salt thereof, and 5 an allosteric carboxylic inhibitor of MMP-13 of Formula IC



or a pharmaceutically acceptable salt thereof, or an N-oxide thereof, in which:

10  $\mathbf{R}_1$  represents a group selected from :

- hydrogen, amino,
- $(C_1-C_6)$ alkyl,  $(C_3-C_6)$ alkenyl,  $(C_3-C_6)$ alkynyl, mono( $C_1-C_6$ )alkylamino( $C_1-C_6$ )alkyl, di( $C_1-C_6$ )alkylamino( $C_1-C_6$ )alkyl, aryl, aryl( $C_1-C_6$ )alkyl, heterocycle, and 3- to 6-membered cycloalkyl( $C_1-C_6$ )alkyl, these groups being unsubstituted or substituted with one or more groups, which may be identical or different, selected from amino,  $(C_1-C_6)$ alkyl, cyano, halo( $C_1-C_6$ )alkyl,  $C(=O)OR_4$ ,  $OR_4$  and  $SR_4$ , in which  $R_4$  represents hydrogen or  $(C_1-C_6)$ alkyl,

15

$\mathbf{W}$  represents an oxygen atom, a sulphur atom, or a group  $=N-R'$ , in which  
20  $R'$  represents  $(C_1-C_6)$ alkyl, hydroxyl, or cyano,

$\mathbf{X}_1$ ,  $\mathbf{X}_2$  and  $\mathbf{X}_3$  represent, independently of each other, a nitrogen atom or a group  $-C-R_6$  in which  $R_6$  represents a group selected from hydrogen,  $(C_1-C_6)$ alkyl, amino, mono( $C_1-C_6$ )alkylamino, di( $C_1-C_6$ )alkylamino, hydroxyl,  $(C_1-C_6)$ alkoxy, and halogen,

25 with the proviso that not more than two of the groups  $\mathbf{X}_1$ ,  $\mathbf{X}_2$  and  $\mathbf{X}_3$  simultaneously represent a nitrogen atom,

**Y** represents a group selected from oxygen atom, sulphur atom, -NH, and -  
N(C<sub>1</sub>-C<sub>6</sub>)alkyl,

**Z** represents:

- an oxygen atom, a sulphur atom,
- 5 • or a group -NR<sub>7</sub> in which R<sub>7</sub> represents a group selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, cycloalkyl, aryl, and heteroaryl, and
- when Y is an oxygen atom, a sulphur atom, or a group -N(C<sub>1</sub>-C<sub>6</sub>)alkyl, Z optionally represents a carbon atom which is
- 10 unsubstituted or substituted with a (C<sub>1</sub>-C<sub>6</sub>)alkyl, an aryl, an aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, an aromatic or non-aromatic heterocycle or a cycloalkyl,

**n** is an integer from 1 to 8 inclusive,

**Z<sub>1</sub>** represents -CR<sub>8</sub>R<sub>9</sub> wherein R<sub>8</sub> and R<sub>9</sub>, independently of each other,

- 15 • represent a group selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, halogen, amino, OR<sub>4</sub>, SR<sub>4</sub> or C(=O)OR<sub>4</sub> in which R<sub>4</sub> represents a hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl, and
- when n is greater than or equal to 2, the hydrocarbon chain Z<sub>1</sub> optionally contains one or more multiple bonds,
- 20 • and/or one of the carbon atoms in the hydrocarbon chain Z<sub>1</sub> may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, or a nitrogen atom which is unsubstituted or substituted with a (C<sub>1</sub>-C<sub>6</sub>)alkyl,
- 25 • and when one of the carbon atoms in the hydrocarbon chain Z<sub>1</sub> is replaced with a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, then the group -C(=Y)-Z- optionally may be absent in the general formula (I),

**A** represents a group selected from :

- aromatic or non-aromatic, 5- or 6-membered monocycle comprising from 0 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, and
- 5      • bicycle, composed of two aromatic or non-aromatic, 5- or 6-membered rings, which may be identical or different, comprising from 0 to 4 heteroatoms selected from nitrogen, oxygen and sulphur,

**m** is an integer from 0 to 7 inclusive,

10      **the group(s) R<sub>2</sub>**, which may be identical or different, is (are) selected from

(C<sub>1</sub>-C<sub>6</sub>)alkyl, halogen, -CN, NO<sub>2</sub>, SCF<sub>3</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -NR<sub>10</sub>R<sub>11</sub>, -OR<sub>10</sub>, -SR<sub>10</sub>, -SOR<sub>10</sub>, -SO<sub>2</sub>R<sub>10</sub>, -(CH<sub>2</sub>)<sub>k</sub>SO<sub>2</sub>NR<sub>10</sub>R<sub>11</sub>, -X<sub>5</sub>(CH<sub>2</sub>)<sub>k</sub>C(=O)OR<sub>10</sub>, -(CH<sub>2</sub>)<sub>k</sub>C(=O)OR<sub>10</sub>,

-X<sub>5</sub>(CH<sub>2</sub>)<sub>k</sub>C(=O)NR<sub>10</sub>R<sub>11</sub>, -(CH<sub>2</sub>)<sub>k</sub>C(=O)NR<sub>10</sub>R<sub>11</sub>, and -X<sub>4</sub>-R<sub>12</sub> in

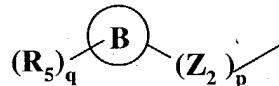
15      which:

- X<sub>5</sub> represents a group selected from oxygen, sulphur optionally substituted by one or two oxygen atoms, and nitrogen substituted by hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl,
- k is an integer from 0 to 3 inclusive,
- 20      • R<sub>10</sub> and R<sub>11</sub>, which may be identical or different, are selected from hydrogen and (C<sub>1</sub>-C<sub>6</sub>)alkyl,
- X<sub>4</sub> represents a group selected from single bond, -CH<sub>2</sub>-, oxygen atom, sulphur atom optionally substituted by one or two oxygen atoms, and nitrogen atom substituted by hydrogen atom or (C<sub>1</sub>-C<sub>6</sub>)alkyl group,

5           •  $R_{12}$  represents an aromatic or non-aromatic, heterocyclic or non-heterocyclic, 5- or 6-membered ring which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from  $(C_1-C_6)$ alkyl, halogen, hydroxyl and amino, and when the ring is heterocyclic, it comprises from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur;

$R_3$  represents a group selected from:

10           • hydrogen,  
          •  $(C_1-C_6)$ alkyl,  $(C_3-C_6)$ alkenyl,  $(C_3-C_6)$ alkynyl, these groups being unsubstituted or substituted with one or more groups, which may be identical or different, selected from amino, cyano, halo( $C_1-C_6$ )alkyl, cycloalkyl,  $-C(=O)NR_{10}R_{11}$ ,  $-C(=O)OR_{10}$ ,  $OR_{10}$ , and  $SR_{10}$ , in which  $R_{10}$  and  $R_{11}$ , which may be identical or different, represent hydrogen or  $(C_1-C_6)$ alkyl,  
15           • and the group of formula :



20           ✓ in which  $p$  is an integer from 0 to 8 inclusive,  
          ✓  $Z_2$  represents  $-CR_{13}R_{14}$  wherein  $R_{13}$  and  $R_{14}$ , independently of each other, represent a group selected from hydrogen,  $(C_1-C_6)$ alkyl, phenyl, halo( $C_1-C_6$ )alkyl, halogen, amino,  $OR_4$ ,  $SR_4$  and  $-C(=O)OR_4$  in which  $R_4$  represents hydrogen or  $(C_1-C_6)$ alkyl, and  
          • when  $p$  is greater than or equal to 2, the hydrocarbon chain  $Z_2$  optionally contains one or more multiple bonds,  
          • and/or one of the carbon atoms in the hydrocarbon chain  $Z_2$  may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, a nitrogen atom which is unsubstituted or substituted with a  $(C_1-C_6)$ alkyl, or a carbonyl group,

- ✓ B represents a group selected from:
  - an aromatic or non-aromatic 5- or 6-membered monocycle comprising from 0 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, and
- 5      • a bicyclic, composed of two aromatic or non-aromatic, 5- or 6-membered rings, which may be identical or different, comprising from 0 to 4 heteroatoms selected from nitrogen, oxygen and sulphur,
- ✓ q is an integer from 0 to 7 inclusive,
- 10     ✓ the group(s) R<sub>5</sub>, which may be identical or different, is (are) selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl, halogen, CN, NO<sub>2</sub>, CF<sub>3</sub>, OCF<sub>3</sub>, -(CH<sub>2</sub>)<sub>k</sub>NR<sub>15</sub>R<sub>16</sub>, -N(R<sub>15</sub>)C(=O)R<sub>16</sub>, N(R<sub>15</sub>)C(=O)OR<sub>16</sub>, -N(R<sub>15</sub>)SO<sub>2</sub>R<sub>16</sub>, -N(SO<sub>2</sub>R<sub>15</sub>)<sub>2</sub>, -OR<sub>15</sub>, -S(O)k<sub>1</sub>R<sub>15</sub>, -SO<sub>2</sub>-N(R<sub>15</sub>)-(CH<sub>2</sub>)<sub>k2</sub>-NR<sub>16</sub>R<sub>17</sub>, -(CH<sub>2</sub>)<sub>k</sub>SO<sub>2</sub>NR<sub>15</sub>R<sub>16</sub>, -X<sub>7</sub>(CH<sub>2</sub>)<sub>k</sub>C(=O)OR<sub>15</sub>, -(CH<sub>2</sub>)<sub>k</sub>C(=O)OR<sub>15</sub>, -C(=O)O-(CH<sub>2</sub>)<sub>k2</sub>-NR<sub>15</sub>R<sub>16</sub>, -C(=O)O-(CH<sub>2</sub>)<sub>k2</sub>-C(=O)OR<sub>18</sub>, -X<sub>7</sub>(CH<sub>2</sub>)<sub>k</sub>C(=O)NR<sub>15</sub>R<sub>16</sub>, -(CH<sub>2</sub>)<sub>k</sub>C(=O)NR<sub>15</sub>R<sub>16</sub>, -R<sub>19</sub>-C(=O)OR<sub>15</sub>, -X<sub>6</sub>-R<sub>20</sub>, and C(=O)-R<sub>21</sub>-NR<sub>15</sub>R<sub>16</sub> in which :
- 15     - X<sub>7</sub> represents a group selected from oxygen atom, sulphur atom optionally substituted by one or two oxygen atoms, and nitrogen atom substituted by a hydrogen atom or a (C<sub>1</sub>-C<sub>6</sub>)alkyl group,
- 20     - k is an integer from 0 to 3 inclusive,
- k<sub>1</sub> is an integer from 0 to 2 inclusive,
- 25     - k<sub>2</sub> is an integer from 1 to 4 inclusive,

- R<sub>15</sub>, R<sub>16</sub> and R<sub>17</sub>, which may be identical or different, are selected from hydrogen and (C<sub>1</sub>-C<sub>6</sub>)alkyl,
- R<sub>18</sub> represents a group selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl, -R<sub>21</sub>-NR<sub>15</sub>R<sub>16</sub>, -R<sub>21</sub>-NR<sub>15</sub>-C(=O)-R<sub>21</sub>-NR<sub>16</sub>R<sub>17</sub>, and -C(=O)O-R<sub>21</sub>-NR<sub>15</sub>R<sub>16</sub> in which R<sub>21</sub> represents a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkylene group, and R<sub>15</sub>, R<sub>16</sub> and R<sub>17</sub> are as defined hereinbefore,
- R<sub>19</sub> represents a (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl group,
- X<sub>6</sub> represents a group selected from single bond, -CH<sub>2</sub>-, oxygen atom, sulphur atom optionally substituted by one or two oxygen atoms, and nitrogen atom substituted by hydrogen atom or (C<sub>1</sub>-C<sub>6</sub>)alkyl group,
- R<sub>20</sub> represents an aromatic or non-aromatic, heterocyclic or non-heterocyclic, 5- or 6-membered ring, which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl, halogen, hydroxyl, oxo, cyano, tetrazole, amino, and -C(=O)OR<sub>4</sub> wherein R<sub>4</sub> represents hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl, and, when the ring is heterocyclic, it comprises from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur,

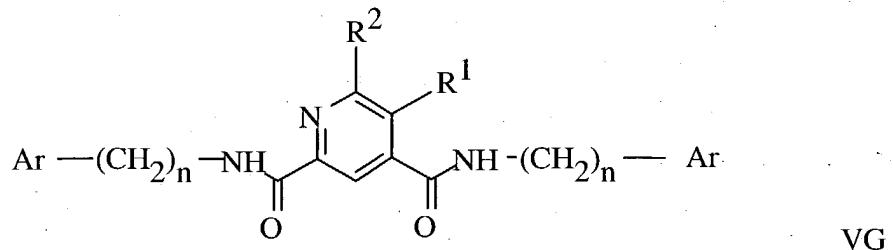
with the proviso that when X<sub>1</sub> represents a nitrogen atom, X<sub>2</sub> cannot represent a carbon atom substituted with a methyl group or with NH-CH<sub>3</sub>.

2. The combination according to Claim 1, wherein the compound of Formula IC is selected from:

4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoic acid;

3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide;  
Methyl 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoate;  
5 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide;  
4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoic acid;  
10 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[2,3-d]pyrimidin-3-ylmethyl]-benzoic acid;  
or a pharmaceutically acceptable salt thereof.

3. A combination, comprising a selective inhibitor of COX-2 that is not celecoxib or valdecoxib, or a pharmaceutically acceptable salt thereof, and  
15 an allosteric carboxylic inhibitor of MMP-13 of Formula VG



or a pharmaceutically acceptable salt thereof, wherein

R<sup>1</sup> and R<sup>2</sup> independently are hydrogen, halo, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, NO<sub>2</sub>, NR<sup>4</sup>R<sup>5</sup>, CN, or CF<sub>3</sub>;

n is 1, and

Each Ar independently is aryl or Het, wherein aryl is phenyl or substituted phenyl, and Het is an unsubstituted or substituted heteroaryl group.

25 4. A pharmaceutical composition, comprising a combination of a selective inhibitor of COX-2 that is not celecoxib or valdecoxib, or a pharmaceutically acceptable salt thereof, and an allosteric carboxylic

inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

5. A method of treating a disease or disorder selected from cartilage damage, inflammation, arthritis, and pain in a mammal, comprising administering to the mammal a therapeutically effective amount of a combination of a selective inhibitor of COX-2 that is not celecoxib or valdecoxib, or a pharmaceutically acceptable salt thereof, and an allosteric carboxylic inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof.  
10
6. The method according to Claim 5, wherein the disease or disorder is rheumatoid arthritis.
7. The method according to Claim 5, wherein the disease or disorder is osteoarthritis.  
15
8. The method according to Claim 5, wherein the disease or disorder is joint inflammation.
- 20 9. The method according to Claim 5, wherein the pain is joint pain.